Lyme Disease in Massachusetts An Update for Health Care Providers 2002

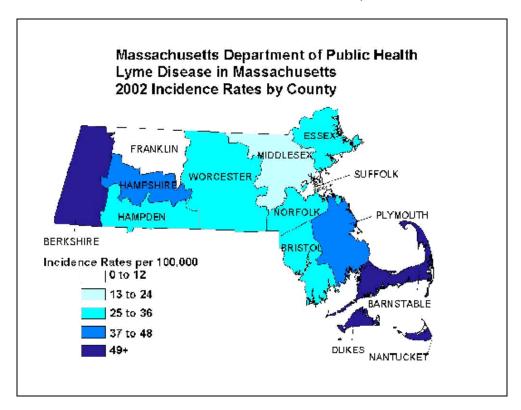
Massachusetts Department of Public Health (MDPH) Division of Epidemiology and Immunization

Introduction

Lyme disease was initially recognized in 1975 during the investigation of an unusual cluster of arthritis cases among children in Lyme, Connecticut. The deer tick, *Ixodes scapularis*, was implicated as the vector for Lyme disease. In 1982, the etiologic agent, *Borrelia burgdorferi*, was first described by, and subsequently named after, Dr. Willy Burgdorfer as a spirochete found in the midgut of the tick. Lyme disease can cause serious musculoskeletal, neurologic or cardiac complications if not recognized early and appropriately treated. It has become the most common vectorborne disease reported in Massachusetts as well as the United States.

Epidemiology

The reported incidence of Lyme disease is greatest in the Northeast, mid-Atlantic, and upper-Midwest regions of the United States. In Massachusetts, the overall incidence rate for 2000 was 18.0 cases per 100,000, which is almost three times the national incidence rate of 6.3 per 100,000. ⁶² The highest incidence of Lyme disease in Massachusetts is found on Cape Cod, southeastern Massachusetts, the islands of Nantucket and Martha's Vineyard, in areas north of Boston, and along the Quabbin Reservoir watershed and the Connecticut River Valley in western Massachusetts.



Between 1990 and 2000, a total of 4, 582 confirmed cases of Lyme disease were reported to the MDPH Surveillance Program, representing 94% of all tickborne diseases reported to the state. Among the 4,519 cases with age reported, the distribution was bimodal and the median age was 38 years (range < 1 - 99 yrs). The two peaks in incidence occurred among children aged 5-9 years (10.2 per 100,000) and adults aged 45-64 years (8.3 per 100,000). Among the 4,558 cases with sex reported, the ratio of male to female was 1:1, however, males had a slightly higher overall incidence rate than females. The majority of cases (51%) was reported during the months of June and July.

Clinical Presentation

The clinical presentation of Lyme disease is protean, including cutaneous, rheumatologic, neurologic and cardiac manifestations. The complex of symptoms and signs can easily lead to confusion with other diseases, particularly if there is no recollection of a tick bite and if the characteristic early skin lesion of erythema migrans is not seen.

Early Lyme disease can be either **localized**, occurring from a few days to a few weeks following exposure, or **disseminated**, occurring sometime after the first week or two following exposure. Recognition of Lyme disease as early as possible is important because prompt initiation of appropriate antibiotic therapy will lead to resolution of infection and the prevention of serious complications.



(Photos courtesy of Lyme Disease Foundation, www.lyme.org)

Localized disease is characterized, in the majority of patients¹⁻⁵, by the appearance of a rash at the site of the tick bite. Photos of some varieties of the rash are shown above. The rash may appear as an erythematous macule or papule, which expands over the course of a few days to form an annular lesion, which can become quite large. The outer border is usually erythematous and flat, with a partial clearing in the middle of the lesion. This is the classic erythema migrans (EM) or

"bull's eye" rash. However, erythema migrans does not always present in this manner. It may appear as an irregular erythematous patch (with or without central clearing), as an oval or triangular erythematous lesion, as an elongated erythematous lesion, or as multiple erythematous lesions. Centrally, the lesion can become very red, indurated and occasionally vesicular or necrotic. However, erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions. In addition to cutaneous manifestations, patients may also experience localized lymphadenopathy and a minor flu-like syndrome characterized by fatigue, low grade fever, headache, arthralgias, and/or myalgias. In approximately one-third of infected persons these flu-like symptoms will occur in the absence of identified erythema migrans. ² It is important for physicians to be familiar with the early signs and symptoms of Lyme disease since many patients will not recall the tick bite at the time of presentation. Left untreated, symptoms may be intermittent and variable during a period of several weeks and infection may progress to disseminated and later stages of disease.

Without treatment, within days to weeks, spirochetes enter the bloodstream and the infection can become established in other organ systems. The **disseminated disease** may progress to manifestations involving multiple organ systems with signs and symptoms that are intermittent, migratory and changing. These signs and symptoms may resolve in several weeks or they may persist and progress in 50% or more of untreated persons. ^{3,9} Some people with Lyme disease may not have had or recognized the early symptoms and, therefore, may present with disseminated manifestations months or even years after their initial infection. Testing for antibody to *B. burgdorferi* in these persons can be helpful, since antibody levels are usually detectable by the time these manifestations occur.

A patient with disseminated infection may have constitutional symptoms of fever and fatigue, which is often profound. There may be multiple EM lesions, diffuse erythema, or urticaria. Myalgias and arthralgias are commonly reported and may be intermittent and migratory. Lymphatic involvement may manifest as regional or generalized adenopathy or splenomegaly. Signs and symptoms of hepatitis, such as right upper quadrant pain and elevated transaminases, may be seen. Respiratory involvement may appear as a sore throat or non-productive cough. The most commonly reported ocular manifestation is conjunctivitis. Iritis, uveitis, optic neuritis, interstitial keratitis, panophthalmitis with loss of vision, and choroiditis with retinal detachment have also been noted. Genitourinary involvement with testicular swelling has been reported.

Without early intervention, **late manifestations** of Lyme disease may become apparent months to years after the initial infection. Arthritis occurs in 25 - 60% of untreated persons with Lyme disease. ^{1,2,15,16} The spectrum of Lyme arthritis ranges from joint pain, to intermittent attacks of overt arthritis, to chronic erosive disease. The arthritis may be mono- or oligo-articular, commonly involves the large joints (most frequently the knee), and is often recurrent with spontaneous remissions and relapses. Lyme arthritis may be confused with other forms of arthritis, particularly if the tick bite was unrecognized and early symptoms were undiagnosed. Attacks of arthritis may last weeks to months and recur for several years; however, the prognosis of those with intermittent arthritis is generally good, with 10-20% spontaneously achieving long-term remission each year. ^{2,15} Synovial inflammation associated with Lyme arthritis may persist in some patients despite eradication of the spirochete with antibiotics. ¹⁷

Neurologic involvement occurs in approximately 10-20% of untreated persons and may include headache and stiff neck (aseptic meningitis), cranial neuropathies (especially facial palsies such as Bell's palsy) and sensory disorders (e.g. paresthesias, dysesthesias), motor radiculopathies, cognitive

dysfunction (e.g. memory loss), or mood changes. ¹⁸⁻²³ These symptoms can fluctuate in severity, may be recurrent, and can overlap with other late manifestations.

Cardiac involvement occurs in approximately 4-8% of untreated persons and may include fluctuating degrees of atrioventricular block (including complete heart block), myopericarditis, and left ventricular dysfunction. ²⁴⁻²⁶ The duration of cardiac abnormalities is usually limited, lasting from 3 days to 6 weeks²⁴, although supportive therapy may necessitate temporary transvenous cardiac pacing in some patients. ²⁵

An atrophic skin disorder, acrodermatitis chronica atrophicans, resulting from chronic inflammation from Lyme disease has been described, as have scleroderma-like skin lesions.²⁷ However, acrodermatitis has been noted primarily in Europe and rarely in the United States.

"Chronic Lyme disease" or "post-Lyme disease syndrome" refers to chronic or intermittent symptoms that may be related to Lyme disease. Although the cause(s) remain uncertain, several possibilities have been suggested: 1) continued active infection that has evaded conventional antibiotic treatment, 2) residual tissue damage resulting from the initial infection, 3) sterile inflammation caused by dead spirochetes remaining in tissue, 4) slowly resolving infection, 5) post-infectious, immune-mediated pathology despite the eradication of the spirochete; and 6) co-infection with another tickborne microorganism. More research is needed to better define this disease entity.

In addition to Lyme disease, there are two other diseases endemic to coastal Massachusetts that are known to be transmitted by the deer tick, babesiosis and ehrlichiosis. The incidence of these diseases in Massachusetts is much lower than the incidence of Lyme disease, however, both can cause life-threatening illness. Physicians should be aware that **coinfection** of *Ixodes scapularis* with two or more of these human pathogens has been reported ⁵³⁻⁵⁴ and may explain the variable clinical manifestations and responses in some patients. ⁵⁵⁻⁵⁶

Pregnancy and Breastfeeding

Concerns have been raised regarding the occurrence of Lyme disease during pregnancy and controversy exists over the risk of adverse outcomes in pregnant women with Lyme disease. Transplacental transmission of *B. burgdorferi* has been reported, but the effects of such transmission on the fetus remain unclear. ⁶³⁻⁶⁴ Congenital Lyme disease, if it occurs at all, is rare. ³³ Presently, there is no conclusive evidence that Lyme disease during pregnancy produces an increase in spontaneous abortions, stillbirths, or fetal abnormalities. ³⁴⁻³⁷ Lyme disease during pregnancy does not appear to cause an increase in childhood neurologic disorders. ³⁸

Women who are pregnant should be counseled on ways to prevent tick exposure and should be promptly treated if suspected of having been infected. The Centers for Disease Control and Prevention (CDC) recommends antibiotic therapy of gestational Lyme disease based on similar guidelines as those for non-pregnant patients, except that doxycycline or probenecid should not be used. More research is needed to define more precisely the risk of Lyme disease during pregnancy and the effects of treatment.

According to the CDC, there is no direct evidence that nursing mothers infected with Lyme disease transmit the infection through their breast milk. Breastfeeding by Lyme disease symptomatic mothers has not been shown to have harmful effects on the infant. ³⁹

Treatment

Standard treatment of early Lyme disease involves the administration of antibiotics for a period of 14-28 days. ⁶⁻⁸ Doxycycline and amoxicillin are the antibiotic drugs of choice for oral therapy, however, doxycycline should not be used in treating children or pregnant women.

Controversy exists in the medical community regarding the appropriate treatment of patients experiencing signs and symptoms consistent with later stages of Lyme disease. ^{6,7,28-30} If a patient is diagnosed as having Lyme disease, a therapeutic regimen that is appropriate to the clinical findings should be chosen. For arthritic, cardiac and neurologic involvement, intravenous therapy with ceftriaxone is often indicated. ⁶⁻⁸ Some studies suggest that prolonged courses of antibiotics may be necessary in certain patients in order to alleviate symptoms. ^{32,57,58} More research is needed to determine the most appropriate type, route of administration and duration of antibiotic therapy for many patients. Some patients with Lyme disease develop manifestations that may not resolve even after antibiotic treatment. ³¹⁻³² These symptoms may include arthralgias, myalgias, arthritis, neuralgia, memory problems or other symptoms not readily distinguished from the multi-symptom complexes seen in chronic fatigue syndrome and fibromyalgia.

A committee appointed by the American College of Rheumatology and the Council of the Infectious Disease Society of America has examined the available evidence and completed a cost-effectiveness analysis for treatment of patients whose only evidence of Lyme disease was a positive immunologic test with no clinical symptoms. They found that empiric treatment of these patients would result in more instances of antibiotic toxicity than cure of asymptomatic disease and would cost as much as \$5,000 per 2-4 week course of intravenous antibiotics. Therefore, the committee concluded that the risks of treatment for these asymptomatic patients outweighed the benefits. ³³

Laboratory Testing

Laboratory confirmation of infection with *B. burgdorferi* is established with isolation of the spirochete from tissue or body fluid. *B. burgdorferi* can be cultured from 80% or more of biopsy specimens taken from early EM lesions; however, the diagnostic usefulness of this procedure is limited because of the need for special bacteriologic methods and protracted observation of cultures. ⁴² In the absence of a culture, a two-step testing algorithm utilizing serologic assays for antibodies is currently recommended by the CDC. ⁴⁵ These assays detect diagnostic levels of IgM and/or IgG antibodies to spirochete antigens in serum or CSF, or a significant change in antibody levels in paired acute- and convalescent- phase samples. These tests are available through commercial laboratories. Regardless of the laboratory you use, be sure that they provide an interpretation of their results.

Polymerase chain reaction (PCR) has been used to amplify genomic DNA of *B. burgdorferi* in skin, blood, CSF and synovial fluid; however, PCR has not been standardized for routine diagnosis of Lyme disease. ⁴² The Lyme urine antigen test (LUAT) is based on an antigen capture-inhibition enzyme linked immunosorbent assay that uses adsorbed polyclonal antibodies that bind to several antigenic moieties. Recent research, however, found this test to be unreliable for the diagnosis of suspected Lyme disease. ⁴³

Serological assays remain the most common and practical method of laboratory testing for Lyme disease. Due to sensitivity and specificity concerns, however, these laboratory tests should only be used to support a clinical diagnosis of Lyme disease. A positive serologic test result may indicate past exposure and be unrelated to a patient's current symptoms or may be the result of cross-reacting antibodies. Since the immune response to spirochetes is relatively slow, serological tests often remain negative for several weeks after exposure. In the event that a patient with

suspected early Lyme disease has a negative serology, serologic evidence of infection is best obtained by testing of paired acute- and convalescent-phase samples. Patients treated early with antibiotics may never seroconvert.

The CDC recommends that specimens be initially analyzed using a sensitive test, such as an enzyme immunoassay (EIA) or immunofluorescent assay (IFA). Samples with positive or equivocal results from these initial tests should be further analyzed using a specific standardized test called a Western blot assay. With the criteria for test positivity in common use at this time, the Western blot assay for anti-*B. burgdorferi* antibodies has higher specificity but lower sensitivity than other methods of detecting antibody responses, such as an EIA or IFA. ⁴⁴ In patients who have previously received the Lyme disease vaccine, a Western blot is recommended as a first test since the vaccine is likely to generate false positive EIA or IFA results. ⁴⁶

The Massachusetts State Laboratory Institute will perform Lyme disease testing by Western blot assay on specimens that are positive or equivocal by a Lyme-specific test, such as an EIA or IFA. Specimens should be submitted with the following information: 1)your name and contact information; 2) patient's name, date of birth and address; 3) clinical symptoms; 4) date of onset; 5) date of collection; 6) laboratory results indicating serologic reactivity compatible with Lyme borreliosis (including assay cut-off and specimen's optical density reading/titer, if applicable); 7) name of Lyme-specific screening test used; and 8) any additional pertinent information, such as treatment status. For questions on where and how to submit samples, please call the State Laboratory at 617-983-6396. Serum and CSF will be tested, but CSF should be accompanied by a serum specimen.

Reporting

Prompt reporting of Lyme disease cases will help identify endemic foci of Lyme disease in Massachusetts and aid in the evaluation of tick control measures. Physicians are required (under regulation 105 CMR 300.100) to report each case of Lyme disease. Physicians can report cases to their local board of health or fax their reports directly to the MDPH Surveillance Program at 617-983-6813. This is a confidential fax.

To make reporting as simple and convenient as possible, physicians can use **either** of two reporting forms developed by MDPH. The multiple case Lyme Disease Reporting Form allows up to five cases from one provider to be reported on a single form. The single case Lyme Disease Reporting Form allows one case per form. Both forms ask for the physician name, patient demographic information, date of diagnosis, and onset date, as well as basic information about clinical presentation. In addition, both forms have areas to record the name of the laboratory where testing was done, if applicable. Additional forms can be obtained from MDPH by calling 617-983-6800.

Because of the absence of a uniform set of diagnostic criteria, the CDC, in association with the Council of State and Territorial Epidemiologists, has developed a national surveillance case definition for Lyme disease. As with other reportable diseases, this definition is intended to be used only by state health departments for epidemiologic surveillance purposes. It should not be used by physicians for clinical diagnosis, management or reporting purposes. MDPH is trying to learn more about the full spectrum of Lyme disease. Therefore, providers should report all cases of diagnosed Lyme disease, regardless of whether they meet the national (CDC) surveillance case definition.

Ecology and Prevention

Deer tick adults and nymphs have a tear-drop shape, eight legs, and are of a relatively small size. The adult female deer tick has a reddish-brown body with a black dorsal shield. Nymphs are the size of a poppy seed. Adults are the size of a sesame seed but may appear larger when engorged.



From left to right: adult female deer tick, adult male deer tick and deer tick nymph shown next to a centimeter ruler. (CDC, www.cdc.gov)

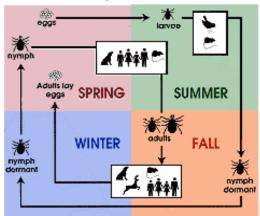


Adult dog tick (not shown to the same scale as deer tick photo) (Iowa State University, www.ipm.iastate.edu)

Dog ticks, by comparison, have a contrasting coloration with a dark brown body and a whitish, patterned dorsal shield. They are somewhat larger, about the size of a watermelon seed, and therefore easier to spot than deer ticks. While not associated with Lyme disease, they are known to transmit other diseases including tularemia and Rocky Mountain spotted fever.

The deer tick life cycle, illustrated on the right, takes two years to complete. Female ticks lay their eggs on the ground in early spring. By summer, eggs hatch into larvae. Larvae prefer to feed on mice, other small mammals and birds in the summer and early fall. They will then molt into nymphs and become inactive until spring. Cold weather (near or below freezing) inhibits tick activity. During the following spring and summer, nymphs will feed on rodents, birds and other small mammals and in the fall they will molt into adults. The adult ticks prefer to feed and mate on large animals, such as deer, in the fall and early spring. Female ticks then drop off these animals and lay up to 2000 eggs on the ground, thus beginning a new life cycle. Nymph and adult ticks are capable of transmitting Lyme disease.

2-Year Life Cycle of the Deer Tick



American Lyme Disease Foundation, www.aldf.com

Educating patients on how they can reduce their risk of contracting Lyme disease is important, particularly if they reside in a high-risk area. Primary preventive measures are related to knowing where and when deer ticks are likely to be found, avoiding such areas or taking precautionary measures, and promptly removing any ticks found attached to the body. In addition to these individual measures, there are steps people can take around their home to reduce the number of ticks on their property.

Ticks cling to vegetation and are most numerous in brushy, wooded or grassy habitats. They are not found on open sandy beaches, but may be found in grassy dune areas. If these areas are unavoidable, patients should be advised to wear light-colored clothing, including long pants tucked into socks or boots and a long-sleeved shirt, and to perform a tick check on themselves after returning indoors. To reduce the number of ticks around their home, people should be advised to

remove leaf litter and brush, move or elevate woodpiles, prune trees and brush to allow in more sunlight, and use fencing to restrict deer.

Ticks do not fly or jump but require direct contact with skin to allow for attachment. Ticks will crawl to the dark, moist areas on the body they prefer, such as the back of the knee, armpit, scalp, groin, and back of the neck. People should pay particular attention to these areas when performing a tick check. The likelihood that an infected tick will transmit the spirochete depends upon the length of time it has been attached and feeding. **The longer the time of attachment, the higher the risk of transmission.** ⁴⁷⁻⁵⁰ Transmission is unlikely if the tick has been attached for less than 24 hours. Therefore, daily tick checks and prompt removal of an attached tick are vital to reducing the risk of transmission.

To remove ticks most effectively, use fine point tweezers to grip the tick as close to the skin as possible. The tick should not be squeezed or twisted, but pulled straight outward with steady, gentle pressure. The application of kerosene, petroleum jelly, nail polish, or a hot match tip to remove a tick should <u>not</u> be used as these measures are ineffective and may result in tick mouthparts remaining embedded in the skin.

While the length of time a tick is attached and taking its blood meal is a critical factor in the likelihood of transmission of Lyme spirochetes and other tickborne pathogens, it may be difficult for patients to recall how long a tick has been attached. Therefore, all persons reporting tick bites should be counseled to monitor themselves for the appearance of rash, fever or other appropriate symptoms and to seek medical evaluation should any signs or symptoms appear. In addition, the administration of antibiotics under certain circumstances may be appropriate (See <u>Prophylactic Antibiotics</u>, p. 9).

Patients may request identification and/or spirochete testing of a tick that was found on them. The following private laboratories will perform both for a fee:

Analytical Services, Inc.
Tick Testing
130 Allen Brook Lane
P.O.Box 515
Williston, VT 05495
1-800-723-4432
www.analyticalservices.com
\$49/tick

Imugen Inc. 220 Norwood Park Norwood, MA 02062 1-800-246-8436 \$45/tick

It is important to counsel patients that these tests are not 100% sensitive or specific. Therefore, even with a negative result, they should monitor themselves for the appearance of rash, fever or other appropriate symptoms and seek medical evaluation should any signs or symptoms appear. If a patient has been infected these signs and symptoms may begin to occur even before the results of tick testing are available. Patients should be advised not to wait for tick testing results before seeking treatment should any signs or symptoms develop. In addition, it should be noted that ticks which test positive may not have transmitted the spirochete.

Use of Repellents and Acaricides

Skin-applicable repellents such as N-N-diethyl-meta-toluamide ("DEET") or clothing-applicable acaricides, such as permethrin, may be used as added protection for persons who cannot avoid high-risk environments. For maximum protection, repellent or acaricide use should always be

combined with the use of personal protective measures such as wearing light-colored clothing including long pants tucked into socks or boots and a long-sleeved shirt, and performing a tick check after returning indoors.

Permethrin, which kills ticks after brief contact, can only be used on clothing. It should be sprayed directly onto the inside and outside of clothing and allowed to dry before the clothing is worn. Permethrin binds very tightly to fabric so very little of it gets onto the skin. Certain formulations can also be used on dogs.

Any repellent or acaricide should be used according to the manufacturer's specifications, since it may be absorbed through the skin and in rare instances cause illness. Patients should be advised to take the following precautions when applying a repellent or acaricide:

- Use just enough to cover exposed skin or clothing;
- Avoid frequent reapplication, which is unnecessary for effectiveness;
- ➤ Never apply on infants or infant clothing;
- ➤ Do not use repellents containing more than 10-15% DEET on children; or those containing more than 30-35% on adults;
- Do not apply to the hands or face of young children;
- Do not apply on cuts, abrasions or sunburned skin; and
- Wash treated skin with soap and water after returning indoors, and launder treated clothing.

While repellents with higher concentrations of DEET may be slightly more effective in discouraging ticks, high concentrations of DEET have been associated with toxicity. The symptoms of DEET toxicity, which are most commonly reported in small children, are headache, mood changes, crying, irritability, confusion, nausea and, very rarely, convulsions and unconsciousness. Some individuals may experience skin irritation or allergic reactions after use of these products.

In Massachusetts, the phone number of the Poison Control Center, which operates 24 hours a day, is 617-232-2120. Outside of the 617 area code, the toll free number is 1-800-682-9211. Specific medical information about the active ingredient in repellents or pesticides may be obtained by calling the National Pesticide Information Center at 1-800-858-7378. You can access their website at <npic.orst.edu>.

While the application of pesticides has been shown to reduce tick populations around individual residential areas ⁵¹⁻⁵², concerns have been raised regarding more widespread use due to unknown long-term effectiveness, environmental contamination, and acaricide resistance.

Prophylactic Antibiotics

The prevalence of infected deer ticks can vary from 15-85% in endemic areas, but the risk of infection after a recognized deer tick bite, even in an endemic area, is estimated to be low⁴⁰. Any patients presenting with a tick bite should be counseled to monitor themselves for the appearance of rash, fever or other appropriate symptoms and to seek medical evaluation should any signs or symptoms appear.

The administration of antibiotics prophylactically after deer tick bites is controversial. A metaanalysis involving data on over 600 people found that antimicrobial prophylaxis was not proven effective, and it estimated that 8 cases of drug-associated rash, including 1 severe life-threatening reaction, would occur for every 10 cases of Lyme disease prevented.⁶¹ A more recent study involving 483 subjects found that a single 200-mg dose of doxycycline, if given within 72 hours after a deer tick bite, was successful in preventing the development of Lyme disease. ⁴¹ This study pointed out several factors which providers should consider prior to administering prophylaxis for a person with a history of a tick bite:

- > timing (the prophylactic treatment needs to be given within 72 hours after the bite);
- > the type of tick (only deer ticks are associated with Lyme disease);
- ➤ the stage of the tick (only the nymphal stage of the tick in this study was associated with infection those in the placebo group bitten by adult ticks did not develop Lyme disease);
- ➤ how long the tick was attached (in most cases, nymphal deer ticks need to be attached for at least 24 hours before transmitting infection. In this study, risk of infection was only found after nymphs had been attached for at least 72 hours); and
- ➤ the geographic area where the tick bit the person (prophylactic treatment after a tick bite should be offered only in high-risk areas).

It is important to remember that many people with Lyme disease don't recall a tick bite, so providers should continue to advise patients to follow appropriate preventive measures (tick checks, protective clothing, repellents, etc.) to prevent tick bites from happening in the first place.

Lyme Disease Vaccine

LYMErixTM, a vaccine for Lyme disease approved in 1998 by the Food and Drug Administration (FDA), was removed from the market by the manufacturer, GlaxoSmithKline Pharmaceuticals, in February 2002. There are no other Lyme disease vaccines approved for use in humans.

References

- Petersen LR., Sweeney AH., Checko PJ., Magnarelli LA., Mshar PA., Gunn RA., Hadler JL. Epidemiological and clinical features of 1, 149 persons with Lyme disease identified by laboratory-based surveillance in Connecticut. Yale Journal of Biological Medicine. 1989; 62(3): 253-262.
- 2. Trock DH., Craft JE., Rahn DW. Clinical manifestations of Lyme disease in the United States. Connecticut Medicine. 1989; 53(6): 327-330.
- 3. Asch ES., Bujak., Weiss M., Peterson MG., Weinstein A. Lyme disease: an infectious and postinfectious syndrome. Journal of Rheumatology. 1994; 21(3): 454-461.
- 4. Gerber MA., Shapiro ED., Burke GS., Parcells VJ., Bell GL. Lyme disease in children in southeastern Connecticut. The New England Journal of Medicine. 1996; 335: 1270-1274.
- 5. Bowen GS., Griffin M., Hayne C., Slade J., Schulze TL., Parkin W. Clinical manifestations and descriptive epidemiology of Lyme disease in New Jersey, 1978-1982. Journal of the American Medical Association. 1984; 251(17): 2236-2240.
- 6. Wormser GP., Nadelman RB., Dattwyler RJ., Dennis DT., Shapiro ED., Steere AC., Rush TJ., Rahn DW., Coyle PK., Persing DH., Fish D., Luft BJ. Practice Guidelines for the Treatment of Lyme Disease. Guidelines from the Infectious Disease Society of America. Clinical Infectious Diseases. 2000; 31 (Suppl 1): S1-14.
- 7. Medical Letter Advisory Board. Treatment of Lyme disease. The Medical Letter. 2000; 42 (1077): 37-39.
- 8. American Academy of Pediatrics. [Lyme Disease Chapter]. In: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectous Diseases. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2000: [p. 377].
- 9. Shadick NA., Phillips CB., Logigian EL., Steere AC., Kaplan RF., Berardi VP., Duray PH., Larson MG., Wright EA., Ginsburg KS., et al. The long term clinical outcomes of Lyme disease. A population based retrospective cohort study. Annuals of Internal Medicine. 1994; 121(8): 560-567.
- 10. Burgdorfer W. Lyme Borreliosis: Ten years after discovery of the etiologic agent, Borrelia burgdorferi. Infection. 1991; 19(4): 257-262.
- 11. Steere AC., Duray PH., Kauffmann DJ., Wormser SP. Unilaterial blindness caused by infection with the Lyme disease spirochete, *B. burgdorferi*. Annuals of Internal Medicine. 1985; 103: 382-384.
- 12. Baum J, Barza M, Weinstein P, Groden J, Aswad M. Bilateral keratitis as a manifestation of Lyme disease. American Journal of Ophthalmology. 1988; 105:75-77.
- 13. Bialasiewicz AA., Ruprecht KW., Naumann GO., Blenk H. Bilateral diffuse choroiditis and exudative retinal detachment with evidence of Lyme disease. American Journal of Ophthalmology. 1988; 105:419-420.
- 14. Steere AC., Bartenhagen NH., Craft JE., Hutchinson GJ., Newman JH., Rahn DW., Sigal LH., Spieler PN., Stenn KS., Malawista SE. The early clinical manifestations of Lyme disease. Annuals of Internal Medicine. 1983; 99(1): 76-82.
- 15. Steere AC., Shoen RT., Taylor E. The clinical evolution of Lyme arthritis. Annuals of Internal Medicine. 1987; 107(5): 725-731.
- 16. Steere AC. Clinical definitions and differential diagnosis of Lyme arthritis. Scandinavian Journal of Infectious Disease. 1991; 77: 51-54.
- 17. Carlson D., Hernandez J., Bloom BJ., Coburn J., Aversa JM., Steere AC. Lack of Borrelia burgdorferi DNA in synovial samples from patients with antibiotic treatment-resistant Lyme arthritis. Arthritis and Rheumatology. 1999; 42(12):2705-2709.
- 18. Cartter ML., Mshar P., Hadler JL. The epidemiology of Lyme disease in Connecticut. Connecticut Medicine. 1989; 53(6): 320-323.
- 19. Nadelman RB., Wormser GP. Lyme borreliosis. The Lancet. 1998; 352(9127): 557-565.

- 20. Pachner AR., Steere AC. The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. Neurology. 1985; 35(1): 47-53.
- 21. Logigian EL., Kaplan RF., Steere AC. Chronic neurologic manifestations of Lyme disease. New England Journal of Medicine. 1990; 323(21):1438-1444.
- 22. Halperin JJ., Luft BJ., Anand AK., Roque CT., Alvarez O., Valkman DJ., Dattwyler RJ. Lyme neuroborreliosis: central nervous system manifestations. Nurology. 1989; 39(6): 753-759.
- 23. Halperin JJ. Neuroborreliosis: central nervous system involvement. Semin Neurol. 1997; 17(1): 19-24.
- 24. Steere AC., Batsford WP., Weinberg M., Alexander J., Berger HJ., Wolfson S., Malawista SE. Lyme cardititis: cardiac abnormalities of Lyme disease. Annuals of Internal Medicine. 1980; 93(1): 8-16.
- 25. Olson LJ., Okafor EC., Clements IP. Cardiac involvement in Lyme disease: manifestations and management. Mayo Clin Proc. 1986; 61(9): 745-749.
- 26. Klein J., Stanek G., Bittner R., Horvat R., Holzinger C., Glogar D. Lyme borreliosis as a cause of myocarditis and heart muscle disease. European Heart Journal. 1991; 12 Suppl D: 73-75.
- 27. Picken RN., Strle F., Picken MM., Ruzic-Sabljic E., Maraspin V., Lotric-Furlan S., Cimperman J. Identification of three species of Borrelia burgdorferi sensu lato (B. burgdorferi sensu stricto, B. garinii, and B. afzelii) among isolates from acrodermatitis chronica atrophicans lesions. Journal of Investigative Dermatology. 1998; 110(3): 211-214.
- 28. Sigal LH. Lyme disease: testing and treatment. Rheumatic Disease Clinics of North America. 1993; 19(1): 79-93.
- 29. Reid MC., Schoen RT., Evans J., Rosenberg JC., Horwitz RI. The consequences of over-diagnosis and over-treatment of Lyme disease: an observational study. Annuals of Internal Medicine. 1998; 128: 354-362.
- 30. Steere AC., Taylor E., McHugh GL., Logigian EL. The overdiagnosis of Lyme disease. Journal of the American Medical Association. 1993; 269 (14): 1812-1816.
- 31. Holt DA., Pattani NJ., Sinnott JT., Bradley E. Lyme Borreliosis. Infect Control Hosp Epidemiol. 1991; 12(8): 493-496.
- 32. Steere AC. Lyme disease. New England Journal of Medicine. 1989; 321(9): 586-596.
- 33. Centers for Disease Control and Prevention. Recommendations for the Use of Lyme Disease Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1999; 48(No. RR-7):[p.4].
- 34. Silver, H.M. Lyme disease during pregnancy. Infectious Disease Clinics of North America 1997; 11(1): 93-97.
- 35. Strobino, B., Abid, S., Gewitz, M., et al. Maternal Lyme disease and congenital heart disease: A case-control study in an endemic area. American Journal of Obstetric Gynecology. 1999; 180: 711-716.
- 36. Maraspin, V., Cimperman, J., Lotric-Furlan, S., et al. Treatment of erythema migrans in pregnancy. Clinical Infectious Diseases. 1996; 22: 788-793.
- 37. Figueroa, R., Bracero, L., Aguero-Rosenfeld, M., et al. Confirmation of *Borrelia burgdorferi* spirochetes by polymerase chain reaction in placentas of women with reactive serology for Lyme antibodies. Gynecol Obstet Invest. 1996; 41: 240-243.
- 38. Gerber, M., Zalneraitis, E. Childhood neurologic disorders and Lyme disease during pregnancy. Pediatric Neurology. 1994; 11: 41-43.
- 39. Ziska, M.H., Giovanello, T., Johnson, M.J., et.al. Disseminated Lyme disease and pregnancy. Conference: 9th Annual International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Boston, MA. April 19-20, 1996.

- 40. Fix, A., Strickland, T., Grant, J. Tick bites in an endemic setting-problematic use of serologic testing and prophylactic antibiotic therapy. JAMA. 1998; 279: 206-210.
- 41. Nadelman RB., Nowakowski J., Fish D., Falco RC. Prophylaxis with a single dose of doxycycline for the Prevention of Lyme disease after an Ixodes scapularis tick bite. New England Journal of Medicine. 2001; 345: 79-84.
- 42. Center for Disease Control and Prevention. Lyme disease: Diagnosis. Posted October 4, 2000. Division of Vector-Borne Infectious Diseases. < www.cdc.gov/ncidod/dvbid/Lymediagnosis.htm >.
- 43. Klempner MS., Schmid CH., Hu L., Steere AC., Johnson G., McCloud B., Noring R., Weinstein A. Intralaboratory reliability of serologic and urine testing for Lyme disease. American Journal of Medicine. 2001; 110: 217-219.
- 44. NCCLS. Western blot assay for antibodies to *Borrelia burgdorferi*; Approved Guideline. NCCLS document M34-A (ISBN 1-56238-415-5). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2000.
- 45. Center for Devices and Radiological Health. FDA Public Health Advisory: Assays for Antibodies to *Borrelia burgdorferi*; Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme disease. Posted July 7, 1997. U.S. Food and Drug Administration. < www.fda.gov/cdrh/lyme.html>.
- 46. Aguero-Rosenfeld, M.E., Roberge, J., Carbonaro, C.A., et. al. Effects of OspA vaccination on Lyme disease serologic testing. J Clin Microbiology. 1999; 37(11): 3718-3721.
- 47. Peavey CA., Lane RS. Transmission of *Borrelia burgdorferi* by *Ixodes pacificus* nymphs and reservoir competence of deer mice (*Peromyscus maniculatus*) infected by tick-bite. Journal of Parasitology. 1995. 81: 175-178.
- 48. Piesman J., Mather TN., Sinsky RJ., Spielman A. Duration of tick attachment and *Borrelia burgdorferi* transmission. Journal of Clinical Microbiology. 1987. 25: 557-558.
- 49. Piesman J., Maupin GO., Campos EG., Happ CM. Duration of adult female *Ixodes dammini* attachment and transmission of *Borrelia burgdorferi* with description of a needle aspiration isolation method. Journal of Infectious Disease. 1991. 163: 895-897.
- 50. Piesman J. Dynamics of *Borrelia burgdorferi* transmission by nymphal *Ixodes dammini* ticks. Journal of Infectious Disease. 1993: 167: 1082-1085.
- 51. Curran KL., Fish D., Peisman J. Reduction of nymphal *Ixodes dammini* (Acari: Ixodidae) in a residential suburban landscape by area application of insecticides. Journal of Medical Entomology. 1993: 30: 107-113.
- 52. Schulze TL., Jordan RA., Vasvary LM et al. Suppression of *Ixodes scapularis* (Acari: Ixodidae) nymphs in a large residential community. Journal of Medical Entomology. 1994: 31: 206-211.
- 53. Levin ML., Fish D. Acquisition of Coinfection and Simulataneous Transmission of *Borrelia burgdorferi* and *Ehrlichia phagocytophila* by *Ixodes scapularis* Ticks. Infection and Immunity. 2000; 68(4): 2183-2186.
- 54. Piesman J., Mather TN., Telford SR., Spielman A. Concurrent *Borrelia burgdorferi* and *Babesia microti* Infection in Nymphal *Ixodes dammini*. Journal of Clinical Microbiology. 1986; 24(3): 446-447.
- 55. Krause PJ., Telford SK III., Speilman A., et al. Concurrent Lyme disease and babesiosis: evidence for increased severity and duration of illness. Journal of the American Medical Association. 1996; 275: 1657-1660.
- Mitchell PD., Reed KD., Hofkes JM. Immunoserologic evidence of coinfection with *Borrelia burgdorferi*, *Babesia microti*, and human granulocytic ehrlichia species in residents of Wisconsin and Minnesota. Journal of Clinical Microbiology. 1996; 34(3): 724-727.

- 57. MacDonald AB., Berger BW., Schwan TG. Clinical implications of delayed growth of the Lyme borreliosis spriochete, *Borrelia burgdorferi*. Acta Tropica. 1990; 48(2): 89-94.
- 58. Schoen RT. Treatment of Lyme disease. Connecticut Medicine. 1989; 53(6): 335-337.
- 59. Steere AC., Malawista SE., Snydman DR., et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connectibut communities. Arthritis and Rheumatology. 1977; 20: 7-17.
- 60. Burgdorfer W., Barbour AG., Hayes SF., Benach JL., Grunwaldt E., Davis JP. Lyme disease-a tick-borne spirochetosis? Science. 1982; 216: 1317-1319.
- 61. Warshafsky, S., Nowakowski, J., Nadelman, R., et al. Efficacy of antibiotic prophylaxis for prevention of Lyme disease. J Gen Int Med. 1996; 11: 329-333.
- 62. Centers for Disease Control and Prevention. Lyme Disease-United States, 2000. MMWR. 2002; 51(2):29-31.
- 63. Schlesinger PA., Duray PH., Burke BA., Steere AC., Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. Annuals of Internal Medicine. 1985; 103: 67-68.
- 64. Weber K., Bratzke HJ., Neubert U., Wilske B., Duray PH. Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatric Infectious Disease Journal. 1988; 7:286-289.

Important Lyme Disease Resources

Lyme Disease in Massachusetts An Update for Health Care Providers, 2002

For further information on Lyme disease or other tickborne diseases, call the Massachusetts Department of Public Health (MDPH), Division of Epidemiology and Immunization at 617-983-6800 or visit the MDPH web site at www.state.ma.us/dph/cdc/epii/lyme/lymehp.htm or the Centers for Disease Control and Prevention (CDC) web site at www.cdc.gov.

For further information on Western blot assays performed by MDPH, call the State Laboratory Institute at 617-983-6396.

To report a diagnosed case of Lyme disease, contact your local board of health or call the MDPH Surveillance Program at 617-983-6801. They will send you a Lyme disease Reporting Form, which, once completed, can be faxed to the MDPH Surveillance Program at 617-983-6813.

For information on having ticks identified or tested for Lyme disease, contact your local extension service or Analytical Services, Inc. at 1-800-723-4432 or Imugen, Inc. at 1-800-246-8436.

For information on the active ingredient in a repellent or pesticide, call the National Pesticide Information Center at 1-800-858-7378.